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SQ-HDM	standardized quality-house dust mite
SOC	System Organ Class (terms per MedDRA)
SPT	skin prick test
TCRS	total combined rhinitis score
TEAE	treatment-emergent adverse event
TEB	Therapeutics Evaluation Branch (DB/ OBPV/ CBER)

Procedure	Visit 1 Screening, Max. 12 Weeks Prior to Day 1	Visit 2 Treatment Day 1*	Telephone Call Treatment Day 8, +/- 1 day	Visit 3[1] Treatment Day 29, +3 days[4]	Telephone Call[2]* Follow-Up Post-Treatment After 5-7 days	Unscheduled Visit[3]
Assess compliance with inclusion/exclusion criteria	X	X	--	--	--	--
Assess AEs since last visit/TC	X[10]	X[11]	X	X	X[12]	X
Provide the subject with a subject card	X	--	--	--	--	--
Provide the *Local and systemic allergic reaction emergency plan* and instruct	--	X	--	--	--	--
Dispense IP and instruct in the use of IP	--	X	(X)[13]	--	--	(X)[14]
Intake of IP at clinic	--	X[14]	--	--	--	
Provide and instruct in the use of the diary	--	X	(X)[15]	--	--	(X)[15]
Collect and evaluate diary	--	--	--	X	--	--
Collect IP, perform compliance check and drug accountability[16]	--	--	--	X	--	--

Source: BLA 125592/157/6, Study MT-18 CSR, Section 9.5.1, Table 6, p. 33.
Abbreviations: AE=adverse event, IP=investigational product
*Visit 2 Treatment=Enrolment & Administration of First Tablet
[1] If a subject discontinues prior to completing the 28-day treatment period, the assessments of V3 should be performed 5-7 days after last IP intake
[2] Post-study treatment with HDM SLIT-tablets must not be initiated before FU-TC has been performed
[3] Assessments at unscheduled visit(s) marked (X) are performed as applicable; Scheduling window is up to 3 days post treatment, Day 28+ (1 to 3) days

- 85.8% of the subjects reported at least 1 IP-related solicited symptom.
- There were no severe IP-related solicited symptoms.

Main results related to unsolicited TEAEs:
- 24.1% of subjects reported at least 1 unsolicited TEAE.
- 15.8% of subjects reported at least 1 IP-related unsolicited TEAE.
- There were no severe IP-related unsolicited TEAEs.

Other safety results:
- There were no SAEs.
- The solicited symptoms reported by the highest proportion of subjects were 'itching of the mouth' (68.4%), 'throat irritation/tickle' (62.1%) and ‘itching in the ear’ (40.7%).
- The IP-related solicited symptoms reported by the highest proportion of subjects (‘itching of the mouth’, ‘throat irritation/tickle’ and ‘itching in the ear’) all had a median onset of 5 minutes after first IP intake.
- The solicited symptoms with the longest median duration (=time between first and last occurrence of that symptom) were ‘itching of the mouth’ (21 days), ‘itching in the ear’ (18 days) ‘throat irritation/tickle’ (16 days). These were also the solicited symptoms reported by the highest proportion of subjects.
- 2 subjects discontinued treatment due to IP-related solicited symptoms or unsolicited TEAEs. 1 subject experienced moderate stomach pain (PT: abdominal pain upper) together with a mild runny nose (PT: rhinorrhea), and 1 subject experienced a moderate sore in the mouth (PT: mouth ulceration). Both subjects recovered from the events/symptoms after treatment discontinuation.
- Of all unsolicited TEAEs that were reported (108 events), 91.6% were mild (99 events), 7.4% were moderate (8 events) and 0.9% were severe (1 event).
- There was 1 severe unsolicited TEAE, which was assessed as unlikely related to IP. The subject recovered with no changes to IP dose.
- 58.3% of the unsolicited TEAEs were assessed as possibly IP-related (63 out of 108 events). Of the IP-related events 93.7% (59 out of 63 events) were assessed as mild and 6.3% (4 out of 63 events) as moderate.
- The most frequently reported unsolicited IP-related TEAEs (reported by ≥2% of subjects) were ‘Oral pain’ (3.2%) and ‘Oral pruritus’ (2.8%).
- 85.8% of subjects reported at least 1 solicited symptom that was assessed as mild, and 10.3% reported at least 1 symptom that was assessed as moderate.

<u>Conclusion: Study MT-18</u>
Prior to completion of MT-18, the safety database included 265 adolescent subjects from different studies with no observations of severe systemic allergic reactions (including anaphylaxis), or severe local swelling/edema of the mouth and/or throat.

Study MT-18 was designed to obtain additional safety data (12 SQ-HDM dose) in adolescents (12 through 17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma to supplement the existing safety database in the age group (12 through 17 years of age). A total of 253 subjects were enrolled to receive treatment with the HDM SLIT-tablet (12 SQ-HDM). The study was conducted according to the study protocol with no deviations impacting the study outcome. The objective of Study MT-18 was to obtain a 1-sided 95% upper confidence limit below 1% for these events in order to exclude the chance of ≥1% of subjects experiencing them. When the safety data from Study MT-18 are added to the overall safety database, this criterion is met. The most common AEs in the study were local allergic reactions related to route of IP

Disposition of adolescent subjects receiving the 12 SQ-HDM dose is shown in Table 14.

Table 14. Study TO-203-3-2: Disposition of Adolescent Subjects 12 through 17 Years of Age Receiving the 12 SQ-HDM Dose (Total Analysis Set)

Disposition	Placebo n (%)	12 SQ-HDM n (%)	Total [a] n (%)
Subjects screened	- (-)	- (-)	454 (-)
Not randomised	- (-)	- (-)	152 (-)
Subjects randomized	99 (-)	107 (-)	302 (-)
Subjects treated	99 (-)	107 (-)	302 (-)
Safety set	99 (100)	107 (100)	302 (100)
Subjects completed	92 (92.9)	99 (92.5)	279 (92.4)
Subjects discontinued	7 (7.1)	8 (7.5)	23 (7.6)
Reason for discontinuation	--	--	--
Adverse event	2 (2.0)	2 (1.9)	6 (2.0)
Lack of efficacy	- (-)	- (-)	- (-)
Physician decision	1 (1.0)	1 (0.9)	2 (0.7)
Pregnancy	- (-)	- (-)	- (-)
Withdrawal by subject	4 (4.0)	5 (4.7)	15 (5.0)
Other	- (-)	- (-)	- (-)

Source: BLA 125592/157/0, ISS, Section 1.2.1.2, Table 1.2.1.2-2, p. 17-18.

In terms of safety monitoring, adverse events (AEs) [name of AE, date of onset, presence/absence of treatment and treatment method, prescription change of IP, seriousness, severity, causal relationship, and outcome] were collected from the start of treatment to the completion of observation after 52 weeks of administration or to the completion of observation on the discontinuation observation day. The following events were also considered AEs (worsening of symptoms because of rhinitis exacerbation was not considered as an AE): for symptoms and signs, occurrence of a new abnormality; for laboratory tests and physiological examinations, clinically significant abnormal changes; any intervention required to treat the worsening of any pre-existing symptoms or laboratory or physiological abnormalities, or judgment of this worsening as medical aggravation. AEs were classified by: Seriousness: “serious” or “non-serious”; Severity: “mild,” “moderate,” or “severe”; Causal relationship: “related,” “possibly related,” or “not related” [AEs classified as “related” or “possibly related” were regarded as “adverse drug reactions (ADRs)”].

A summary of AE types for all treatment arms in subjects 12 through 64 years of age is provided in Table 15.

- Of the 946 subjects in the study, 820 subjects (86.7%) experienced AEs and 453 subjects (47.9%) experienced ADRs.
- No deaths occurred.
- SAEs occurred in 13 subjects (1.4%). A causal relationship to IP was ruled out for all these SAEs.
- Other significant AEs (excluding SAEs) were asthma in 8 subjects (0.8%).
- Adverse events (excluding SAEs and asthma) leading to IP discontinuation occurred in 14 subjects (1.5%), and ADRs leading to IP interruption occurred in 33 subjects (3.5%).

- One event of anaphylactic reaction occurred as an SAE in 1 subject in the placebo group.

Table 15. Study TO-203-3-2: Summary of Adverse Events in Subjects 12 through 64 Years of Age

Parameter	Placebo (n=319) N (%)	6 SQ-HDM (n=313) N (%)	12 SQ-HDM (n=314) N (%)	Active All (n=627) N (%)	Overall (n=946) N (%)
Adverse event	256 (80.3)	280 (89.5)	284 (90.4)	564 (90.0)	820 (86.7)
Adverse drug reaction	54 (16.9)	199 (63.6)	200 (63.7)	399 (63.6)	453 (47.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse event	3 (0.9)	5 (1.6)	5 (1.6)	10 (1.6)	13 (1.4)
Serious adverse drug reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other important adverse event (excluding SAE)	14 (4.4)	20 (6.4)	19 (6.1)	39 (6.2)	53 (5.6)
Anaphylactic reaction[*1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma[*2]	3 (0.9)	3 (1.0)	2 (0.6)	5 (0.8)	8 (0.8)
Adverse events leading to discontinuation[*3]	6 (1.9)	4 (1.3)	4 (1.3)	8 (1.3)	14 (1.5)
Adverse drug reactions leading to interruption[*4]	5 (1.6)	14 (4.5)	14 (4.5)	28 (4.5)	33 (3.5)

Source: BLA 125592/157/0, Study TO-203-3-2 CSR, Section 12.2.1, Table 12.2-1, p. 132.
Abbreviations: N: Number of subjects with events, %: Incidence
[*1]: Excepted serious adverse events (Anaphylactic reaction occurred as a serious adverse event: 1 subject in the placebo group)
[*2]: Not occurred asthma as serious adverse event
[*3]: Except discontinuation subjects due to serious adverse event and asthma (Serious adverse event leading to discontinuation: 1 subject in the placebo group, 1 subject in the 12 SQ-HDM group; subjects with asthma leading to discontinuation: 2 subjects in the placebo group, 3 subjects in the 6 SQ-HDM group)
[*4]: No interruption due to anaphylactic reaction and asthma occurred
Quotation from 14.3.1.2 (reposted)

The number of common adverse reactions and the number of subjects with common adverse reactions are shown by age in Table 16. The adverse reactions whose incidence in adolescent subjects (younger than 18 years of age) was ≥2% higher than that in adult subjects (18 through 64 years of age) were: oral pruritus (difference: 6.2%), oropharyngeal discomfort (difference: 4.6%), and mouth edema (difference: 3.4%). The adverse reactions whose incidence in adult subjects (18 through 64 years of age) was ≥2% higher than that in adolescent subjects (younger than 18 years of age) were: ear pruritus (difference: 3.9%) and throat irritation (difference: 3.1%). No major differences in the incidence of common adverse reactions were found between adolescent subjects (younger than 18 years of age) and adult subjects (18 through 64 years of age).

addition to HDM), duration of HDM-induced AR/C, asthma status and asthma duration, ICS use at baseline, baseline IgE levels, and baseline HDM wheal size. Regardless of age group, most subjects were white and approximately 20% of subjects were Black or African American or multi-racial. Most subjects were sensitized to 1 or more allergens in addition to HDM (76% of subjects in both age groups). All subjects had HDM-induced AR/C, and the duration of HDM-induced AR/C (number of years) was similar across treatment groups within each age group (a mean duration of 8.3 years among the adolescents and 20.1 years among the adults). Subjects were included in P001 based on a serum-specific IgE to HDM (*D. farinae* or *D. pteronyssinus*) of at least 0.7 kU/L, and for 20% of adolescents and 32% of adults, the highest HDM-specific IgE level was in the range of 0.7 to <3.5 kU/L. Within each age group, no major differences between treatment groups were observed with respect to baseline IgE levels.

Across age groups, only minor differences were noted; in the adolescent age group females comprised a smaller proportion of subjects, the HDM-specific IgE levels were higher (specifically, 27% of adolescents had an HDM-specific IgE level in the range of 50 to 100 kU/L or greater compared to 6% of adults), and the proportion of subjects with asthma at baseline was higher (40% of adolescent subjects reported asthma at baseline compared to 30% of adults, with no differences between treatment groups in either age group), as compared to the adult age group.

Study TO-203-3-2

Across age groups, the treatment groups were well-balanced with respect to demographics (except race, as all subjects in this study were Asian). Most adolescent subjects were male (62%) while most adult subjects were female (65%), with no significant differences between treatment groups in either age group. The age distribution was similar across treatment groups for adolescents as well as adults. Within age groups, the treatment groups were well balanced with respect to age, gender, baseline sensitizations (HDM only vs other sensitizations in addition to HDM), duration of HDM-induced AR/C, and baseline IgE levels. All subjects had HDM-induced AR/C, and the duration of HDM-induced AR/C (in years) was similar across treatment groups within each age group (mean duration of 6.2 years among adolescents and 11.8 years among adults).

Across age groups, only minor differences were noted; in the adolescent age group females comprised a smaller proportion of subjects and the HDM-specific IgE levels were higher, as compared to the adult age group.

In contrast to Study P001, only Asian subjects were included, and patients with asthma or ICS use were excluded. Additionally, the inclusion criterion on specific IgE to HDM was different in this study (serum IgE level ≥ 3.5 kU/L) as compared to Study P001 (serum IgE level ≥ 0.7 kU/L) and accordingly, a higher proportion of subjects in the higher baseline IgE classes (serum IgE ≥ 50 to 100 kU/L or greater) was noted as compared to Study P001. In Study TO-203-3-2, for most adult subjects (78%) the highest HDM-specific IgE level was in the range of 3.5 to 17.5 kU/L or 17.5 to 50 kU/L, whereas most adolescent subjects (88%) had an HDM-specific IgE level in the range of 17.5 to 100 kU/L or greater.

> *Reviewer Comment:*
> *A limitation of this study, from a single study standpoint, was that all subjects were Asian. However, since Asians are often underrepresented in studies*

Source: BLA 125592/157/0 and 6, Study TO-203-3-2 CSR, Section 9.5.1.4.5; P001 CSR, Appendix 16.1.1, Table 8; Study P008 CSR, Appendix 16.1.1.1, Table 5; Study MT-03 CSR, Section 5.7.1; Study MT-18 CSR, Section 9.5.2.1.

Causality

For causality assessments of AEs in this sBLA, IP-related AEs were defined as:

- Study MT-03: events reported as “possibly related” by the investigator
- Study P008, P001: events reported as "related" by the investigator
- Study TO-203-3-2: events reported as "possibly related" or "related" by the investigator
- Study MT-18: events reported as "possibly related" by the investigator

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Pooled safety data should be interpreted with caution.

Studies P001 and MT-18 are the only studies that utilized a Side Effect Report Card to solicit adverse reactions for the first 28 days. Unsolicited adverse events were recorded for the entire study duration.

All other studies recorded unsolicited adverse events.

8.4 Safety Results

A summary of TEAEs in adolescents who received Odactra 12 SQ-HDM or placebo from the five clinical studies in which adolescents were evaluated (Studies MT-03, P008, P001, MT-18, and TO-203-3-2) is shown in Table 19.

Table 19. Studies MT-03, P008, P001, MT-18, and TO-203-3-2: Summary of Treatment-Emergent Adverse Events in Adolescent Subjects 12 through 17 Years of Age in (Safety Analysis Set)

Characteristic	Odactra 12 SQ-HDM (N=522) N (%)	Placebo (N=262) N (%)
Subjects with one or more AEs	452 (86.6)	187 (71.4)
Intensity	--	--
Mild	444 (85.1)	177 (67.6)
Moderate	80 (15.3)	45 (17.2)
Severe	7 (1.3)	3 (1.1)
Unknown	61 (11.7)	4 (1.5)
No AEs	70 (13.4)	75 (28.6)
With drug-related AEs	413 (79.1)	80 (30.5)
With serious AEs	0	2 (0.8)
With serious drug-related AEs	0	0
Discontinued due to an AE	17 (3.3)	3 (1.1)
Discontinued due to a drug-related AE	17 (3.3)	1 (0.4)
Discontinued due to a serious AE	0	1 (0.4)
Discontinued due to a serious drug-related AE	0	0
Deaths	0	0

Source: BLA 125592/157/16, Response to FDA IR#10, Table 1, p. 3.
Abbreviations: AE= adverse event, SQ-HDM=Standardized Quality- House Dust Mite (unitage), N: number of subjects, (%): percentage of subjects in population.
Subjects who discontinued, discontinued both the study and the treatment.

System Organ Class Adverse Reaction (Any Intensity‡)	**Odactra (N=253)**
Tongue pain	19.0%
Nausea	17.4%
Stomach pain	16.6%
Swelling of the tongue	15.4%
Diarrhea	10.3%
Vomiting	2.8%
Nervous system disorders	--
Food tasting different	8.3%
Respiratory, Thoracic, and Mediastinal disorders	--
Throat irritation/tickle	62.1%
Throat swelling	14.6%

Source: Adapted from BLA 125592/157/6, ISS, Section 2.1.2, Table 2.1.2.6-1, p. 79.
Abbreviations: n=number of subjects, %=percentage of subjects in safety set.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of SLIT) were those reported by subjects within the first 28 days after treatment initiation.
†The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, edema uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).
‡No severe solicited adverse reactions were reported.

Reviewer Comment:
A comparison of the solicited adverse reactions in adolescents from Study P001 and Study MT18 reveals that all 15 pre-specified solicited adverse reactions occurred in both studies and that most of the adverse reactions were reported at a slightly lower frequency by subjects/ investigators in Study MT-18. Of note, in Study P001, the report card/diary prompted subjects to record 'Yes' or 'No' as to whether they experienced any of the 15 pre-specified symptoms/signs of SLIT within 60 minutes of taking the IP or placebo, whereas in Study MT-18 no specific time limit for reporting after taking the IP was specified.

The adverse reactions that were reported at similar rates between the two studies were swelling of the uvula/ back of the mouth, swelling of the lips, and nausea.

The adverse reactions that were reported at higher rates in Study MT-18 were: tongue ulcer/ sore on the tongue, mouth ulcer/ sore in the mouth, diarrhea, and taste alteration/ food tasting different.

Unsolicited Adverse Events

Most Frequently Reported Unsolicited TEAEs (reported by at least 2% of subjects in any 12 SQ-HDM group)

Study P001
Overall, the pattern of the most frequently reported unsolicited TEAEs, both with regards to type of reported events and the frequency by which they were reported, was similar across age groups. Across age groups, the overall proportion of subjects reporting the most frequent TEAEs was higher in the 12 SQ-HDM treatment group (94% of adolescents, 87% of adults) as compared to placebo (68% of adolescents, 58% of adults). Across age groups, the most frequently reported TEAEs were among the symptoms/signs which were solicited during the first 28 days of treatment. The most

IP-Related TEAEs

Study P001
Overall, the pattern of unsolicited IP-related TEAEs, both with regards to type of events and frequencies by which the events were reported, was similar across age groups.

Across age groups, the overall proportion of subjects reporting an IP-related TEAE as well as the total number of reported TEAEs was higher in the 12 SQ-HDM treatment group as compared to the placebo group. Similarly, the proportion of subjects discontinued due to an IP-related TEAE was higher in the 12 SQ-HDM treatment group as compared to the placebo group. The vast majority of all IP-related TEAEs were mild or moderate in severity and the proportion of 12 SQ-HDM-treated subjects reporting severe, IP-related TEAEs was the same in both age groups (2%).

Across age groups, the most frequently reported IP-related TEAEs were all local reactions related to study product administration and reported by a higher proportion of subjects in the 12 SQ- HDM treatment group as compared to the placebo group. In the 12 SQ-HDM treatment group, the most frequently reported IP-related TEAEs were the same (adolescents; adults); 'oral pruritus' (73%; 60%), 'throat irritation' (69%; 61%), 'ear pruritus' (50%; 50%). These 3 treatment-related TEAEs were also among the most frequently reported TEAEs in adolescent and adult subjects in the placebo group.
All of the most frequently reported IP-related TEAEs were solicited symptoms/signs.

Study MT-18
Sixteen percent of the subjects reported an unsolicited IP-related TEAE. The majority of these were mild in severity, a few were moderate, and no events were severe. No unsolicited IP-related SAEs were reported. The proportion of subjects discontinuing due to an unsolicited IP-related TEAE was low which was similar to Study TO-203-3-2 and lower than Study P001. In Study MT-18, 1 subject discontinued the study due to an unsolicited IP-related TEAE. In total, 2 subjects discontinued the study due to unsolicited IP-related TEAEs or solicited symptoms. The most frequently reported unsolicited IP-related TEAE (reported as ≥2% subjects with the event) were local reactions related to IP administration: ‘oral pain’ (3%) and ‘oral pruritus’ (3%).

Study TO-203-3-2
Overall, the pattern of IP-related TEAEs, both with regards to type of events and frequencies by which the events were reported, was similar across age groups.

Across age groups, the proportion of subjects reporting an IP-related TEAE as well as the total number of reported TEAEs was higher in the 12 SQ-HDM treatment group as compared to the placebo group. The vast majority of all events were mild in severity, a few were moderate and no events in either age group were severe. No IP-related SAEs were reported. Across age and treatment groups, the proportion of subjects discontinuing due to an IP-related TEAE was low and the proportion of adolescent subjects in the 12 SQ-HDM treatment group discontinuing due to an IP-related TEAE was similar to in Study MT-18 and lower than in Study P001.

Across age groups, the most frequently reported IP-related TEAEs were all local reactions related to IP administration and reported by a higher proportion of subjects in the 12 SQ-HDM treatment group as compared to the placebo group. In the 12 SQ-HDM treatment group, the most frequently reported IP-related TEAEs were the same

(adolescents; adults); 'oral pruritus' (22%; 15%) and 'throat irritation' (13%; 11%). One difference between the adolescent and adult age groups was that 'oropharyngeal discomfort' was reported by a higher proportion of adolescent subjects (11%) as compared to adult subjects (3%).

8.4.5 Clinical Test Results

Not applicable, as no overall clinical laboratory evaluations were performed as there was no blood collection at the end of study and thus, no comparisons to baseline values were possible.

8.4.6 Systemic Adverse Events

For this sBLA, systemic adverse events were denoted as severe and systemic events of interest and were defined (with the term 'treatment-related' used synonymously with the term 'IP-related') as:

- IP-related systemic allergic reactions (both when identified directly by investigators and when identified as per the modified Sampson criteria)
    - the assessment of systemic allergic reactions was based on pooled data from all adolescent subjects exposed to 12 SQ-HDM or placebo and the events were identified by 2 measures:
        - events directly reported by investigators were identified using the SMQ 'Anaphylactic reaction', narrow terms
        - events fulfilling the modified Sampson criteria were identified through medical evaluation of co-occurring events identified using the SMQ 'Anaphylactic reaction', broad term algorithm
- IP-related events treated with epinephrine
- IP-related severe local swelling or edema of the mouth/throat.

Data on severe and systemic events of interest for the 12 SQ-HDM dose (n=522) or placebo (n=270) are presented across all adolescent subjects included in any of the 5 studies in which adolescent subjects were exposed to 12 SQ-HDM (Table 22). In the population of 522 adolescent subjects exposed to 12 SQ-HDM, the observed rates were 0% for all three sub-categories of the severe and systemic events of interest.

Based on these observed rates, the upper bound of the 95% CI of the incidence proportion of all combined severe and systemic events of interest is 0.70% for the 12-SQ-HDM treatment group and 1.4% for the placebo treatment group, respectively.

> *Reviewer Comment:*
> *Although the point estimate for the incidence of severe and systemic events of interest is 0% in the studies conducted in adolescents, the calculated 95%CI range suggests that there is a 95% chance that the incidence of these events would fall into the range of 0 and 0.7% in subjects receiving Odactra as the number of observations (number of subjects/ patients receiving Odactra) increases beyond the number of observations in these pre-licensure studies. Taking the total number of subjects in each group into account, the confidence interval calculations in Table 22 were verified.*

Table 22. Studies MT-03, P008, P001, TO-203-3-2, MT-18: Incidence of Severe and Systemic Adverse Events of Interest in Adolescents in All Adolescents Exposed to Odactra 12 SQ-HDM or Placebo (Safety Analysis Set)

Severe and Systemic Events of Interest	12 SQ-HDM (N=522) n (%) 95% CI	Placebo (N=270) n (%) 95% CI
IP-related Systemic Allergic Reactions	--	--
Directly reported by investigator [a]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
Based on modified Sampson criteria [b]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
IP-related Events treated with Epinephrine	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
IP-related severe local swelling or edema of the mouth/throat [c]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
Total Severe and Systemic Events of Interest	**0 (0) [0.0%; 0.7%]**	**0 (0) [0.0%; 1.4%]**

Source: BLA 125592/157/6, SCS, Section 2.1.5.3, Table 24, p. 72.
Abbreviations: n=number of subjects with event, %n=percent subjects of safety set, N=number of subjects in safety set, CI=confidence interval.
[a.] Based on MedDRA SMQ 'Anaphylactic reaction' narrow terms.
[b.] Based on medical evaluation of co-occurring events identified through MedDRA SMQ 'Anaphylactic reaction' broad terms, for fulfilment of the criteria for anaphylaxis according to Sampson et al. 2006.
[c.] Events identified via the PTs: Dysphagia, Dysphonia, Epiglottic edema, Laryngeal dyspnea, Laryngeal obstruction, Laryngeal edema, Laryngotracheal edema, Mouth swelling, edema mouth, Oropharyngeal edema, Oropharyngeal swelling, Palatal edema, Palatal swelling, Pharyngeal edema, Pharyngeal swelling, Sensation of foreign body, Suffocation feeling, Swollen tongue, Throat tightness, Tongue edema, Tracheal edema.

The following is a list of adverse events within each of the sub-categories (for Studies P001, MT-18, and TO-203-3-2) that were excluded from Table 22 (rationale included in the brief narratives below):

- IP-related systemic allergic reactions (both when identified directly by investigator and when identified as per modified Sampson criteria)
    - Study P001:
        - One adolescent subject treated with 12 SQ-HDM reported a systemic allergic reaction (PT 'anaphylactic reaction') not considered IP-related by the investigator. The subject had a medical history of peanut allergy and reported the event after eating a cookie containing peanuts. The event was moderate in severity, non-serious and the subject recovered from the event.
        - A total of 20 subjects were identified to have reported 65 co-occurring events, i.e., events affecting at least 2 organ systems, with the same start date, based on the SMQ 'Anaphylactic reaction' broad term algorithm. After medical evaluation of these co-occurring events, no events were evaluated to fulfil the criteria for diagnosis of anaphylaxis as per modified Sampson criteria, thus, the observed rate of IP-related systemic allergic reactions as per modified Sampson criteria was 0%.
    - Study MT-18: One adolescent subject taking 12 SQ-HDM experienced mild urticaria for 15 minutes and mild swelling in the back of the mouth for 5 minutes on Day 3 of treatment. Both events resolved spontaneously without the use of any rescue medication, and IP treatment was

continued. As the localization (i.e., local vs. systemic) of the event of urticaria was unknown, it could not be excluded that the subject experienced a systemic allergic reaction, and medical evaluation identified this as a possible systemic allergic reaction (see Section 6.1.12.5) (this event was not reported in the SCS or ISS or Table 22 as this event was not characterized to be “of interest” due to spontaneous resolution of the events).

- IP-related events treated with epinephrine
  - Study TO-203-3-2: One subject treated with 12 SQ-HDM reported epinephrine use due to an event of mild 'pharyngitis'. This event was not considered IP-related by the investigator.
- IP-related severe local swelling of the mouth and /or throat with the potential to compromise airways
  - no events were reported

8.4.7 Local Reactogenicity

See Section 8.4.4, as most of the common adverse events were local in nature.

8.4.8 Adverse Events of Special Interest

AESIs were defined as: IP-related systemic allergic reactions including anaphylaxis (see Section 8.4.6 above), IP-related events treated with epinephrine (see Section 8.4.6 above), IP-related severe local swelling/ edema of the mouth and/or throat (see Section 8.4.6 above), as well as IP-related EoE (reported here in this section).

Eosinophilic esophagitis (EoE)
Due to the concern for EoE in subjects taking SLIT products, selected upper gastrointestinal tract AEs were reviewed.

EoE was not assessed in the Phase I studies (MT-03 and P008).

There were no cases of EoE identified in Study MT-18 or Study TO-203-3-2.

Two cases reporting an adolescent subject undergoing evaluation for EoE, 1 taking Odactra 12 SQ-HDM and 1 taking placebo, were identified in Study P001. These events are summarized below.

1. One 13-year-old subject taking Odactra 12 SQ-HDM in Study P001 was diagnosed with EoE on Day 204 based on an upper endoscopy showing 10-20 eosinophils per high powered field in both the mid and distal esophagus. The subject was treated with swallowed fluticasone, omeprazole, and continued in the study.
2. One 14-year-old subject taking placebo was evaluated for potential EoE via a stomach biopsy on Day 198 that showed 30 eosinophilic per high powered field. The subject was treated with high dose lansoprazole. A repeat endoscopy on Day 296 showed no eosinophils in the mid or distal esophagus and only 2 eosinophils per high powered field in the proximal esophagus. The subject was ultimately diagnosed with gastroesophageal reflux disease. This subject completed the study.

Clinical Benefit	• Phase 3 Study P001 was a double blind, randomized, controlled, field efficacy and safety study evaluating Odactra for a treatment duration of 12 months in adolescents and adults 12 through 85 years of age. Although it is uncertain whether the treatment effect of Odactra is maintained beyond one or multiple courses of treatment, the post-hoc efficacy analysis in the adolescent population resulted in a relative treatment difference of the total combined rhinitis score for active treatment compared to placebo of -22.4% (95% CI: -42.6%, -8.1%).	• Although, the duration of effectiveness on therapy beyond one year and effectiveness after discontinuation of Odactra have not been characterized, a therapeutic benefit was seen over a treatment period of 12 months. • The totality of evidence for treatment with Odactra in adolescents 12 through 17 years of age supports its' effectiveness for treatment of HDM-induced AR/C and suggests clinically meaningful benefit. • SLIT may be disease-modifying.
Risk	• The most substantial risks of treatment with Odactra are life-threatening local (e.g., pharyngeal edema) and systemic allergic reactions including anaphylaxis. However, these events were rare (in Phase 3 studies in adolescents, these adverse events occurred at a rate of 0%). • The most common adverse reactions occurring in ≥ 10% of adolescent subjects in Studies P001 and MT-18 were throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Most reactions were mild to moderate in severity and resolved relatively quickly and without sequelae. • In the clinical studies in adolescents of 1 year duration (P001 and TO-203-3-2), one adolescent subject taking Odactra (12 SQ-HDM) developed EoE.	• The risk of serious systemic allergic reaction with Odactra is low. • Local reactions are common, but generally mild to moderate and self-limited. • EoE is known to be associated with SLIT products. Further studies are needed to characterize the incidence of EoE in patients taking SLIT products. • The safety profile of Odactra in adolescents is acceptable and is justified by the clinical benefit.
Risk Management	• The Odactra PI includes a boxed warning about severe allergic reactions. • A prescription for injectable intramuscular epinephrine for emergency treatment of systemic allergic reactions should be given to any individual for whom Odactra is prescribed; patients should be educated on the technique of epinephrine auto-injector self-administration. • Patients should be warned about the potential risk of eosinophilic esophagitis and directed to contact a health care professional if any signs or symptoms of eosinophilic esophagitis occur.	• Use of product labeling (PI and MG) and the PVP plan to communicate the potential for serious local adverse reactions, severe systemic allergic reactions, and EoE and to educate patients or parents/ guardians on how to manage these risks could adequately mitigate the risk of local adverse reactions, systemic allergic reactions, and EoE.

itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Based on the submitted data, the risks of treatment with Odactra appear to be modest and adverse reactions tend to be self-limited. However, because of the small risk of systemic allergic reactions and local allergic reactions, patients should be prescribed auto-injectable epinephrine. In addition, while 1 case of EoE was noted to occur in the adolescent populations evaluated, EoE remains a known risk with sublingual AIT products. To mitigate this risk, product labeling (PI and MG) is used to communicate the potential for development of EoE.

While the duration of treatment effect after discontinuation of Odactra has not been studied, the addition of Odactra as the first sublingual AIT product for treatment of perennial HDM allergy to the currently available treatments for HDM allergy provides another treatment option for adolescents 12 through 17 years of age with HDM-induced AR/C in the U.S. that is effective with an acceptable safety profile and that is possibly less burdensome than currently available treatment options. Given the clinical benefit associated with the consistent treatment effect and the modest risks of treatment with Odactra observed in Studies P001, MT-18, and TO-203-3-2, the overall risk-benefit assessment for Odactra is favorable for its intended use in the adolescent population.

11.3 Discussion of Regulatory Options

Although Study MT-18 had limitations (28 days in duration, lack of placebo comparator given the open-label study design, descriptive analyses), the safety data from this study and from Study TO-203-3-2 supplement the existing safety database for Odactra in the adolescent population (existing safety database for adolescents from Study P001). The safety and efficacy profile of Odactra was established in 1279 adults 18 through 65 years of age in 4 double-blind, placebo-controlled, randomized clinical studies. In addition, Odactra has been licensed in the U.S. for use in persons 18 through 65 years of age since 2017, and the safety of Odactra has been evaluated in post-marketing studies (these data are described in the currently approved PI for Odactra).

Overall, the safety data from Studies P001, MT-18 and TO-203-3-2 and the efficacy data from Study P001 are sufficient to support approval of Odactra for immunotherapy for HDM-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites or by skin testing to licensed HDM allergen extracts in adolescents 12 through 17 years of age; therefore, consideration of other regulatory options was not necessary.

11.4 Recommendations on Regulatory Actions

The data submitted to this supplemental BLA support licensure of Odactra in adolescents 12 through 17 years of age.

11.5 Labeling Review and Recommendations

CBER recommended, and the Applicant agreed to, several revisions to the PI intended to clarify and more clearly describe the clinical data in the adolescent population. Section 6 Adverse Reactions was revised to display safety data in the adolescent population from Study P001 and Study MT-18 separately from adult data from clinical

studies conducted in the adult population. Specific revisions to Section 6 resulted in inclusion of solicited adverse reaction data (for the first 28 days after initial administration of Odactra) and unsolicited adverse reaction data for the duration of the studies (as opposed to unsolicited adverse event data over 28 days) for the adolescent population from Study P001 and Study MT-18. The MG was revised to include adverse events in adolescents 12 through 17 years of age. Language in the PI and MG was adapted from adults only to include adults and adolescents (and their parents/guardians).

Since EoE is known risk associated with SLIT products, the PI lists EoE under Section 5 Warnings and Precautions. Although the occurrence of systemic allergic reactions including anaphylaxis observed in pre-licensure clinical studies was not common, treatment with Odactra may require use of epinephrine. For this reason, the PI includes a Black Box Warning and a MG, both of which emphasize the potential risk for severe allergic reactions and need for access to auto-injectable epinephrine.

The PI submitted by the Applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" to establish requirements for Pregnancy and Lactation Labeling.

11.6 Recommendations on Post-Marketing Actions

Additional post-marketing safety studies are not recommended. Routine pharmaco-vigilance measures are adequate.